

Diagnosis and management of primary biliary cholangitis: perspectives versus evidence

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I read with great interest the correspondence of Dr. Zavos [1] regarding our recently published consensus statements of the Hellenic Autoimmune Liver Diseases Study Group (HALDSG) on primary biliary cholangitis (PBC) [2], and the respective 2026 updated guidance on PBC treatment of the Associazione Italiana per lo Studio del Fegato (AISF) [3]. I do not agree that both statements were based on the same evidence, as the HALDSG report was based on strict, objective and distinct scientific criteria that have been used for many years by several authorities, including the European Association for the Study of the Liver [4]. The AISF guidelines, on the other hand, are more like an excellent in-depth review than actual real guidance, because there are no clear-cut suggestions, whereas supporting levels of evidence and—most importantly—indications as to the grading of statements (strong or weak/open) are missing.

More specifically, the HALDSG paper was based on the famous criteria of the Oxford Centre for Evidence-based Medicine (OCEBM) (Table 1). All statements, including the grading and level of evidence, were subject to thorough discussions and approval by all the 7 core panel members during several zoom meetings and numerous email communications, looking internally for an almost 100% consensus ($\geq 6/7$ agreement among core panel members). Subsequently, the draft statements were submitted to 32 Delphi members of

HALDSG for independent review and voting, resulting in 63 statements—all with strong consensus—after revision of the text according to their comments and the Journal's external review process.

This major difference in methodology makes a comparison between the two manuscripts impossible. Another obstacle in the AISF paper is that it deals only with PBC treatment, even though it is generally well known in medicine that before treatment initiation you need a prompt, firm and timely diagnosis for a disease that is largely unrecognized, as it depends significantly on the commitment of the laboratory to the guidelines [5,6].

On the other hand, the supposed superior performance of the Rete Sicilia Selezione Terapia (RESIST) criteria (platelets $\geq 120 \times 10^9/L$ and serum albumin ≥ 3.6 g/dL) over Baveno VII for ruling out clinically significant portal hypertension (CSPH)—actually only by the presence or not of varices [7]—particularly in those with ALP levels higher than $1.5 \times$ upper limit of normal (ULN), should be treated cautiously. This was a cross-sectional retrospective study, with a relatively low number of patients classified as having low-risk CSPH according to Baveno VII, which does not allow the extrapolation of conclusions about the prognostic role of noninvasive tests in predicting evolutionary events during follow up, while there were no hepatic venous pressure gradient measurements in an attempt to confirm the hypothesis of RESIST's superiority. In addition, so far, the RESIST criteria have not been externally validated in PBC patients, while the possibility of unsatisfactory reproducibility of endoscopy-based diagnosis and grading of varices as an indicator of CSPH has not been considered. Therefore, for the RESIST criteria we need properly designed prospective studies to improve and validate the accuracy of the results.

Table 1 Levels of evidence (A) and grades of recommendations (B) based on the Oxford Centre for Evidence-based Medicine (Adapted from: [2])

A		
Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (SR) (with homogeneity) of randomized-controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	RCT or observational studies with dramatic effects; SR of lower quality studies (i.e., non-randomized, retrospective)	
3	SR of lower quality studies (i.e., non-randomized, retrospective)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (SR are generally better than individual studies)	
5	Expert opinion (Mechanism-based Reasoning)	Any estimate of effect is uncertain
B		
Grade	Wording	Criteria
Strong	Must, shall, should, is recommended Shall not, should not, is not recommended	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested May not, is not suggested	

For all these reasons the core panel members decided to endorse the most popular and well supported data of the Baveno VII recommendations [8], even though it was realized that early prediction of the presence of CSPH—and not only of high-risk varices as the recent study assessed [7]—remains an unsolved medical need in PBC patients.

Regarding treatment, the endorsement by the AISF of adequate response (ALP between 1.1 and 1.5 × ULN or 1.1 and 1.67 × ULN), as an acceptable target in asymptomatic patients over 62 years with liver stiffness <10 kPa [3], seems rational, but it cannot quite be supported sufficiently, as we do not have robust prospective follow-up data on this specific subgroup of patients—only a single retrospective study [9]. This is why our statement on deep or complete response was particularly emphasized for high-risk PBC patients (defined not only by age and liver stiffness) [2]. Taking everything together, this AISF suggestion, though rational, should be cautiously treated as quite arbitrary, while in my opinion, individualized management should be applied in this subgroup of patients, involving the evaluation of more risk factors, as some of them may potentially experience detrimental consequences.

Evidence guides a roadmap in an attempt to solve patients' problems by providing objective recommendations/statements based on available reported documentation (level of evidence). In this effort a clear-cut methodology design should be clearly and precisely included—such as the OCEBM criteria in the current HALDSG report [2]. In contrast, perspectives represent subjective and/or personal viewpoints to interpret the data, shaped by beliefs and life experiences, but in general, they cannot really be proven. From my point of view, this is the major difference between the two recently published papers on PBC management [2,3].

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